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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US98/24458 <b>(22) International Filing Date:</b> 17 November 1998 (17.11.98)  <b>(30) Priority Data:</b> 60/066,197                      19 November 1997 (19.11.97)      US  <b>(71) Applicant (for all designated States except US):</b> HUMANETICS CORPORATION [US/US]; Interchange Tower, Suite 1205, 600 South Highway 169, St. Louis Park, MN 55425-1205 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> WEEKS, Charles, E. [US/US]; 5276 Lakeview Avenue, White Bear Lake, MN 55110 (US).  <b>(74) Agent:</b> SHERRILL, Michael, S.; Michael S. Sherrill Law Offices, Suite 200, 4756 Banning Avenue, White Bear Lake, MN 55110-3205 (US).		<b>(81) Designated States:</b> AU, CA, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> USE OF $\Delta 5$ -ANDROSTENE- $3\beta$ -OL-7,17-DIONE IN THE TREATMENT OF ARTHRITIS  <b>(57) Abstract</b>  Arthritis can be treated by administering therapeutic amounts of $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione and metabolizable precursors thereof, such as $\Delta 5$ -androstene- $3\beta$ -acetoxy-7,17-dione, which are readily metabolized <i>in vivo</i> to $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione but are not appreciably metabolizable <i>in vivo</i> to androgens, estrogens or dehydroepiandrosterone. Such treatment can be prophylactic, ameliorative or curative in nature.		

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**USE OF  $\Delta^5$ -ANDROSTENE-3 $\beta$ -OL-7,17-DIONE  
IN THE TREATMENT OF  
ARTHRITIS**

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**FIELD OF THE INVENTION**

This invention broadly relates to treatment strategies for arthritis. More specifically, the invention relates to prophylactic, ameliorative and curative drug therapies for arthritis.

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**BACKGROUND**

Arthritis is a collective term for number of different conditions that cause pain, swelling and limited movement in joints and connective tissue throughout the body. Specific causes for arthritis are not yet known for most forms of the disease. The condition is usually chronic. The main symptoms of arthritis are joint pain, joint stiffness or inability to move a joint normally, and sometimes swelling that lasts more than two weeks. Most treatment programs include a combination of medication, exercise, rest, use of heat and cold, joint protection techniques, and sometimes surgery.

20

The three most prevalent forms of arthritis are osteoarthritis (OA), fibromyalgia (FM), and rheumatoid arthritis (RA).

25

Osteoarthritis (OA) is a degenerative joint disease characterized by a breakdown of the joint's cartilage. Cartilage functions to cushion the ends of the bones at each joint. A breakdown of the cartilage causes the bones to rub against each other, causing pain and loss of movement. OA primarily affects hands and weight-bearing joints, such as the knee, hips, feet and back. Risk factors for OA include advanced age, obesity, joint injury, and genetic disposition. Suggested causes for OA include an abnormal release of destructive enzymes from the cartilage cells

30

themselves, and inherent defects in the way joints fit together. Most people over 60 suffer from OA, but only about one-third of those over 60 exhibit symptoms of OA.

Conventional treatment of OA focuses on decreasing pain and improving joint  
5 movement. Medications include aspirin, acetaminophen, ibuprofen and nonsteroidal anti-inflammatory drugs (herein after NSAIDs) for pain relief and inflammation reduction. Corticosteroid injection directly into affected joints in acute cases is also employed. Other noninvasive techniques commonly used to control OA include heat/cold treatment, exercise, joint protection and weight control.

10

Fibromyalgia (FM) is manifest as widespread pain affecting muscles and attachments to the bone. The patient may also exhibit tender points, specific areas that hurt when pressure is applied. Other symptoms can include fatigue, sleep disturbances, migraine headaches, irritated bowel syndrome, chest pain and nervous  
15 system symptoms such as depression.

Conventional treatment of FM include use of medications including aspirin, acetaminophen, ibuprofen or NSAIDs for pain relief and inflammation reduction.

20 Rheumatoid arthritis (RA) is an inflammatory disease having many components, including an autoimmune disorder aspect. The autoimmune disorder aspect is generally characterized by inflammation of the membrane lining the joint resulting from an attack upon the joint by the body's own immune system. The inflammation causes pain, stiffness, warmth, redness and swelling. The inflamed joint  
25 lining, call the synovium, can invade and damage surrounding bone and cartilage. The involved joint can lose shape and alignment, resulting in pain, loss of movement and possible destruction of the joint. Early in the disease, people may notice general fatigue, soreness, stiffness and aching. Pain usually occurs in the same joints on both sides of the body and will usually start in the hands or feet. RA can also affect wrists,  
30 elbows, shoulders, neck, knees, hips and ankles. Other symptoms include lumps, called rheumatoid nodules, under the skin in areas subjected to pressure, such as the back of elbows.

RA can be diagnosed by a laboratory test for rheumatoid factor, an abnormal substance found in the blood of about 80% of adults with RA. However the presence or absence of rheumatoid factor does not in itself indicate that one has RA. An  
5 overall pattern of symptoms, medical history and physical examination are also used in diagnosing RA.

Conventional treatment of RA focuses on reducing swelling, relieving pain and stiffness, and maintaining normal joint function. Medications include NSAIDs  
10 for controlling inflammation, joint pain, stiffness and swelling. Disease-modifying drugs include low doses of prednisone, methotrexate, hydroxychloroquine, azulfidine, gold salt and cyclosporin, used alone or in combination. Some combination of exercise, rest, medication, joint protection, physical and occupation therapy, and surgery is also used to treat RA patients.

15

RA is characterized by striking age-sex disparities. The incidence of RA in women increases steadily from the age of menarche to its maximal incidence around menopause. The disease is uncommon in men under age 45, but its incidence increases rapidly in older men and eventually approaches the incidence in women.  
20 These observations strongly suggest that androgens may play some role in RA. Dehydroepiandrosterone (DHEA), an adrenal product, is the major androgen precursor in men and women. Its production is dependent upon age, peaking in the 2<sup>nd</sup> and 3<sup>rd</sup> decades in women. DHEA levels are low in both men and women with RA, and recent data show that levels of this hormone may be depressed before onset of the  
25 disease. The menopausal peak of RA onset suggests estrogen and/or progesterone deficiency may also play a role in the disease. RA typically remits during pregnancy, in parallel with increasing levels of corticosteroids, estrogens and progesterone. Oral contraceptives, which generate a condition of pseudopregnancy, also decrease the risk of RA. These data argue that adrenal and gonadal steroid hormones affect the  
30 development of RA. In addition, several studies indicate that corticosteroid production is inappropriately low in patients with RA.

Traditional treatment regimens for arthritis, including medications for reducing tissue inflammation, often meet with limited success. Hence, the search continues for alternative treatments for arthritis patients.

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#### SUMMARY OF THE INVENTION

The invention is directed to the prophylactic, ameliorative and curative treatment of arthritis by administering  $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione and precursors thereof which are readily metabolized *in vivo* to  $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione but essentially incapable of being metabolized to androgens, estrogens or dehydroepiandrosterone.

15

#### DETAILED DESCRIPTION OF THE INVENTION INCLUDING A BEST MODE

Arthritis can be treated by administering therapeutic amounts of  $\Delta 5$ -androstene- $3\beta$ -ol-7,17 dione and precursors thereof which are readily metabolized *in vivo* to  $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione but essentially incapable of being metabolized to androgens, estrogens or dehydroepiandrosterone, such as  $\Delta 5$ -androstene- $3\beta$ -acetoxy-7,17 dione and other  $3\beta$  esters thereof.

25

Such treatment can be prophylactic, ameliorative or curative in nature.

#### $\Delta 5$ -Androstene- $3\beta$ -ol-7,17-dione

$\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione is a derivative of dehydroepiandrosterone (DHEA) which does not appreciably stimulate, increase or otherwise enhance the production of sex hormones.  $\Delta 5$ -androstene- $3\beta$ -ol-7,17 dione is commercially available from a number of sources including Steraloids, Inc. of Wilton, New Hampshire. A number of procedures are available for synthesizing  $\Delta 5$ -androstene- $3\beta$ -

ol-7,17 dione from DHEA, with one such procedure described in United States Patent No. 5,296,481.

Precursors of  $\Delta^5$ -androstene-3 $\beta$ -ol-7,17-dione, other than DHEA, may also be usefully employed in the treatment of arthritis. Such precursors are readily metabolized *in vivo* to the active  $\Delta^5$ -androstene-3 $\beta$ -ol-7,17-dione. One example of such a metabolizable precursor is the commercially available  $\Delta^5$ -androstene-3 $\beta$ -acetyl-7,17-dione. The 3 $\beta$ -acetyl group is readily hydrolyzed *in vivo* by esterases located in the blood and various body tissue to produce the active  $\Delta^5$ -androstene-3 $\beta$ -ol-7,17-dione, and is believed to be less susceptible to oxidation at the 3-position during the manufacturing process relative to  $\Delta^5$ -androstene-3 $\beta$ -ol-7,17-dione.

## Administration

### *Administration Route*

The  $\Delta^5$  Androstene-3 $\beta$ -acetoxy-7,17-dione can be administered by virtually any of the commonly accepted practices for the administration of pharmaceutical preparations including specifically, but not exclusively, intravenous injection, mucosal administration, oral consumption, ocular administration, subcutaneous injection, transdermal administration, etc.

Mucosal administration of  $\Delta^5$  Androstene-3 $\beta$ -acetoxy-7,17-dione includes such routes as buccal, endotracheal, inhalation, nasal, pharyngeal, rectal, sublingual, vaginal, etc. For administration through the buccal / inhalation / sublingual / pharyngeal / endotracheal mucosa, the steroid may be formulated as an emulsion, gum, lozenge, spray, tablet or an inclusion complex such as cyclodextrin inclusion complexes. Nasal administration is conveniently conducted through the use of a sniffing powder or nasal spray. For rectal and vaginal administration the steroid may be formulated as a cream, douch, enema or suppository.



Oral consumption of the steroid may be effected by incorporating the steroid into a food or drink, or formulating the steroid into a chewable or swallowable tablet or capsule.

5

Ocular administration may be effected by incorporating the steroid into a solution or suspension adapted for ocular application such as drops or sprays.

Intravenous and subcutaneous administration involves incorporating the steroid into a pharmaceutically acceptable and injectable carrier.

10

For transdermal administration, the steroid may be conveniently incorporated into a lipophilic carrier and formulated as a topical creme or in an adhesive patch.

15

### ***Dose Rate***

The range of dosages and dose rates effective for achieving the desired biological properties and characteristics may be determined in accordance with standard industry practices. These ranges can be expected to differ depending upon whether the desired response is the prophylactic, ameliorative or curative treatment of arthritis, the specific type of arthritis and the severity of symptoms.

20

**EXPERIMENTAL****Experiment 1**

*(Preparation of  $\Delta^5$  Androstene-3 $\beta$ -acetoxy-7,17-dione)*

5

***Step One:***

*(Preparation of  $\Delta^5$  Androstene-3-acetoxy-17-one)*

A suitable, three-necked, round-bottom flask equipped with an overhead stirrer,  
10 reflux condenser, solids addition funnel and 110-volt temperature controller was  
charged with a mixture of dichloromethane (90 ml), glacial acetic acid (150 ml), and  
acetic anhydride (250 ml). To the mixture was added dehydroepiandrosterone (0.20  
moles) purchased from Steraloids, Inc. of Wilton, New Hampshire. The mixture was  
stirred to dissolve the solid dehydroepiandrosterone, and anhydrous sodium acetate (35.0  
15 g) added. The resulting mixture was heated at 75°C with stirring for 3 hours to  
complete the reaction.

The reaction mixture was poured into one liter of water and the resulting slurry  
stirred at room temperature for 2 hours. The organic dichloromethane layer was  
20 separated from the aqueous layer, and the aqueous layer extracted once with 50 ml of  
fresh dichloromethane. The combined organic dichloromethane extract was washed  
with water, saturated sodium bicarbonate solution (until neutral), and water. The  
resulting washed organic dichloromethane extract was evaporated under reduced  
pressure to a volume of 40 ml. Methanol (100 ml) was added to this concentrated extract  
25 and the resulting solid mass was cooled at 0°C in a refrigerator for 2 hours.

The resulting solid white product was collected by vacuum filtration on a  
Buchner funnel and the filter cake air dried on the funnel to form a first crop of product  
weighing 50.5 g. The filtrate mother liquor was concentrated by evaporation under  
30 reduced pressure, and cooled at 0°C in a refrigerator. The resulting solid white product  
was collected by vacuum filtration on a Buchner funnel and the filter cake air dried on  
the funnel to form a second crop of product weighing 10.2 g. The filtrate mother liquor

from the second crop of product was diluted with water and the mixture was cooled at 0°C in a refrigerator. The resulting solid white product was collected by vacuum filtration on a Buchner funnel and the filter cake air dried on the funnel to form a third crop of product weighing 4.2 g.

5

The first, second and third crops of product were combined to produce a total of 64.9 grams of  $\Delta^5$  androstene-3-acetoxy-17-one.

10

Theoretical yield	=	66.1 g
First crop yield	=	50.5 g (76.4%)
Second crop yield	=	10.2 g (15.4%)
Third crop yield	=	4.2 g (6.4%)

**Step Two:**

15

*(Preparation of Crude  $\Delta^5$  Androstene-3-acetoxy-7,17-dione)*

20

A suitable, three-necked, round-bottom flask equipped with an overhead stirrer, reflux condenser, addition funnel, thermometer, mineral oil filled bubbler and a gas inlet tube connected to a nitrogen cylinder, was charged with acetone (3.5 L) and cyclohexane (3.5 L). 1.51 moles of the  $\Delta^5$  Androstene-3-acetoxy-17-one prepared in Step One was added to the flask with stirring to dissolve the solid  $\Delta^5$  Androstene-3-acetoxy-17-one. 2.48 moles of solid sodium metaperiodate and water (1.1 L) were added to the stirred solution. 14.75 moles of a 70% aqueous solution of *t*-butyl hydroperoxide (2.0 L) was added to the flask through the addition funnel over a one-half hour period.

25

Over the first hour, the reaction mixture temperature rose from 20°C to 32°C. Tap water was added to an external cooling bath and the reaction mixture temperature returned to 20°C. The reaction mixture was constantly vigorously stirred throughout the experiment, and the reaction judged to be complete after 48 hours by TLC monitoring of the disappearance of starting material. The mixture changed from a white slurry to a light yellow slurry over the course of the reaction.

30

The reaction mixture was poured into a stirred ice/water mixture (12 kg ice and 8 L water). Potassium sulfite (3 L of a 45% aqueous solution) was then added to the diluted reaction mixture over 30 minutes (100mL/min) to destroy any remaining  
5 oxidant. The diluted mixture was stirred for an additional 2 hours, with ice added as needed to maintain the mixture at 15°C.

The resulting diluted, cooled reaction mixture was transferred to a suitable container and ethyl acetate (3 L) was added to dissolve and extract the product. The  
10 ~~resultant mixture was stirred for one-half hour and then allowed to stand so as to permit~~  
the organic and aqueous layers to separate. The aqueous layer was examined by TLC, found to contain no product, and discarded. The solids containing organic layer was transferred to a separatory funnel, washed with water (3 x 1.5 L), then washed with a saturated salt solution (1 x 1.5 L). The washed organic layer was dried over sodium  
15 sulfate (300 g), with decolorizing carbon (100 g) added. The resulting organic slurry was filtered through a ceramic Buchner funnel containing a 0.5 inch Celite pad (100 g). The filter cake was washed with ethyl acetate (2 x 150 ml) and the washing combined with the filtrate.

20 The combined organic filtrate was concentrated *in vacuo* to near dryness to produce an off-white semi-solid. The semi-solid was suspended in methanol (400 ml) and again concentrated *in vacuo* to near dryness to produce a semi-solid. The semi-solid was slurried in methanol (600 ml) and the slurry stirred for 2 hours at ambient temperature. The solid product was collected by filtration on a ceramic Buchner  
25 funnel, and the solids washed with cold (5°C) methanol (2 x 75 ml). The solid product was dried at 65°C for 48 hours under high vacuum (<1 mm Hg vacuum). The process yielded 232 grams of crude solid  $\Delta^5$  Androstene-3-acetoxy-7,17-dione.

	Theoretical yield	=	521 g
30	Actual yield	=	232 g (44.5%)

*Step Three:**(Preparation of Purified  $\Delta^5$  Androstene-3-acetoxy-7,17-dione)*METHOD A:

5

A 500 ml round bottom flask equipped with a magnetic stirrer was charged with 25.0 grams of the crude  $\Delta^5$  Androstene-3-acetoxy-7,17-dione prepared in Step Two and 300 ml of a mixture of methanol and ethyl acetate (1:1, v/v). The magnetic stirrer was activated and the slurry stirred at room temperature until the crude  $\Delta^5$  Androstene-3-  
10 acetoxy-7,17-dione was completely dissolved in the solvent mixture to form a first solution. A freshly prepared 10% aqueous solution of sodium bicarbonate (25 ml) was added over 10 minutes to the reaction mixture. The resulting milky mass was stirred at room temperature for 2.5 hours.

15

The reaction mixture was concentrated at room temperature under reduced pressure to 100 ml volume. The concentrated reaction mixture was diluted with 200 ml of ice water and stirred for 30 minutes at 0-5°C. The precipitated solids were collected on a ceramic Buchner funnel, and the aqueous filtrate reserved for additional product recovery. The solids on the funnel were washed with water (until neutral), and methanol  
20 (2 x 30 ml), with the methanol washing also reserved for product recovery. The first crop of solids was dried overnight under vacuum to give 18.0 g of purified product.

25

The aqueous filtrate from the first crop of solids was extracted with ethyl acetate (100 ml), and the separated organic extract was washed with water. The solvent of the  
25 washed extract was removed under reduced pressure to produce a solid product. This solid product was dissolved in the methanol washing from the first crop of solids, and the solution concentrated to 30 ml volume. Upon cooling the concentrate, a solid precipitate product formed which was collected by vacuum filtration. The second crop of solids was air dried to give 5.2 g of purified product.

30

The mother liquor filtrate from the second crop of solids was diluted with water and cooled. The resulting white solid precipitate was collected by vacuum filtration, and dried overnight at room temperature to give a third crop of 1.0 g of purified product.

5        The process yielded a total of 24.2 grams of purified solid  $\Delta^5$  Androstene-3-acetoxy-7,17-dione.

Theoretical recovery = 25.0 g

Actual recovery = 24.2 g (96.8%)

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METHOD B:

A suitable round bottom flask equipped with a magnetic stirrer was charged with 1.0 gram of the crude  $\Delta^5$  Androstene-3-acetoxy-7,17-dione prepared in Step Two and 10  
15 ml of acetone. The magnetic stirrer was activated and the slurry was stirred at room temperature until the crude  $\Delta^5$  Androstene-3-acetoxy-7,17-dione was completely dissolved in the acetone. To this solution was added 2.0 g of aluminum oxide basic. The resulting slurry was stirred at room temperature for 1 hour, then filtered through a bed of Celite. The collected solids and Celite bed were washed once with 5 ml of  
20 acetone, and the washing combined with the filtrate. The combined filtrate was evaporated to near dryness under reduced pressure to produce a solid product. The solid product was dissolved in a mixture of methanol and isopropyl ether (8:2, v/v) with heating. This solution was cooled at 0-5°C for 30 minutes, resulting in precipitation of a white product. The precipitated solid was collected by vacuum filtration and air dried to  
25 give 0.9 grams of purified solid  $\Delta^5$  androstene-3-acetoxy-7,17-dione.

Theoretical recovery = 1.0 g

Actual recovery = 0.9 g (90.0%)

30

I claim:

1. A treatment method comprising treating an arthritis affected patient in need of such treatment with an effective tissue inflammation ameliorative amount of a steroid selected from  $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione and metabolizable precursors thereof incapable of being appreciably metabolized to androgens, estrogens or dehydroepiandrosterone.
2. The treatment method of claim 1 wherein the method comprises treating an arthritis affected patient with an effective amount of a tissue inflammation ameliorative amount of a steroid selected from  $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione and  $\Delta 5$ -androstene- $3\beta$ -acetoxy-7,17-dione.
3. The treatment method of claim 1 or 2 wherein the method of treating an arthritis affected patient comprises treating an arthritis affected human patient.
4. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating a human patient afflicted with osteoarthritis.
5. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating a human patient afflicted with fibromyalgia.
6. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating a human patient afflicted with rheumatoid arthritis.
7. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating an arthritis affected patient afflicted with arthritis-related tissue inflammation.

8. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating a human patient diagnosed with osteoarthritis.
9. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating a human patient diagnosed with fibromyalgia.
10. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating a human patient diagnosed with rheumatoid arthritis.
11. The treatment method of claim 3 wherein the method of treating an arthritis affected human patient comprises treating an arthritis affected patient diagnosed with arthritis-related tissue inflammation.
12. A treatment method comprising administering an effective arthritis-related tissue inflammation preventative amount of a steroid selected from  $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione and metabolizable precursors thereof incapable of being appreciably metabolized to androgens, estrogens or dehydroepiandrosterone to a patient susceptible to arthritis-related tissue inflammation.
13. The treatment method of claim 12 wherein the method comprises treating a patient susceptible to arthritis-related tissue inflammation with an effective arthritis-related tissue inflammation preventative amount of a steroid selected from  $\Delta 5$ -androstene- $3\beta$ -ol-7,17-dione and  $\Delta 5$ -androstene- $3\beta$ -acetoxy-7,17-dione.



14. The treatment method of claim 12 or 13 wherein the method of treating a patient susceptible to arthritis-related tissue inflammation comprises treating a human patient susceptible to arthritis-related tissue inflammation.
15. The treatment method of claim 14 wherein the method of treating a patient susceptible to arthritis-related tissue inflammation comprises treating a human patient afflicted with osteoarthritis.
16. The treatment method of claim 14 wherein the method of treating a patient susceptible to arthritis-related tissue inflammation comprises treating a human patient afflicted with fibromyalgia.
17. The treatment method of claim 14 wherein the method of treating a patient susceptible to arthritis-related tissue inflammation comprises treating a human patient afflicted with rheumatoid arthritis.
18. The treatment method of claim 14 wherein the method of treating a patient susceptible to arthritis-related tissue inflammation comprises treating a human patient diagnosed with osteoarthritis.
19. The treatment method of claim 14 wherein the method of treating a patient susceptible to arthritis-related tissue inflammation comprises treating a human patient diagnosed with fibromyalgia.
20. The treatment method of claim 14 wherein the method of treating a patient susceptible to arthritis-related tissue inflammation comprises treating a human patient diagnosed with rheumatoid arthritis.
21. The treatment method of claim 14 wherein the method of treating an arthritis affected human patient comprises treating a human patient diagnosed with osteoarthritis.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/24458

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 45/00; A61K 31/56

US CL :514/169, 177, 178, 179, 180, 181, 182

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/169, 177, 178, 179, 180, 181, 182

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstract, Volume 106, abstract No. 143992, RAYMOND F. PEAT, "Pharmaceutical Compositions Containing Dehydroepiandrosterone and other Anesthetic Steroids in the Treatment of Arthritis and Other Joint Disabilities", US 4,528,052 A, 09 December 1986, see entire abstract.	1-21
Y	Chemical Abstract, Volume 126, abstract No. 113708, HENRY A. LARDY, "Treatment of Immune System With .DELTA.5 Androsterones", US 5,585,371 A, 17 December 1996, see entire abstract.	1-21

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